Recommendations of *Arixtra* Use in the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines

This information is provided in response to your request for information about Arixtra® (fondaparinux sodium).

SUMMARY

- The American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines for Antithrombotic and Thrombolytic Therapy recommendations are categorized as being either strong (Grade 1) or weak (Grade 2) followed by an assessment of the quality of evidence. High quality, moderate quality and low quality is denoted as A, B and C respectively.
- GlaxoSmithKline does not contribute to or endorse the ACCP Evidence-Based Clinical Practice Guidelines for Antithrombotic and Thrombolytic Therapy.
- Important safety information is found in the attached Prescribing Information.
- The prescribing information for this product contains a boxed warning. Please consult the WARNING section of the attached prescribing information for further details and for important safety information.

THE AMERICAN COLLEGE OF CHEST PHYSICIANS (ACCP) EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES FOR ANTITHROMBOTIC AND THROMBOLYTIC THERAPY: RECOMMENDATION(S)

The American College of Chest Physicians (ACCP)[1] has developed independent evidence-based guidelines for the use and monitoring of antithrombotic and thrombolytic therapies to help clinicians make decisions for typical patients about prevention or treatment of arterial or venous thromboembolic disease. The following summary of the ACCP guidelines is not intended to be all inclusive. Please see the full ACCP guidelines for further information at http://www.chestjournal.org/content/vol133/6_suppl/. GlaxoSmithKline does not contribute to or endorse the ACCP guidelines.

A standardized process has been adopted by the ACCP for the methodology used for guideline development, including grading of their recommendations. This system entails an initial assessment of the quality of the evidence, followed by judgment about the direction and strength of the recommendations. Recommendations are categorized as being either strong (Grade 1) or weak (Grade 2), followed by an assessment of the quality of the evidence. Grade 1, a strong recommendation by ACCP, means that ACCP is confident that benefits do or do not outweigh harms, burdens, or costs. Therefore, Grade 1 recommendations can be applied uniformly to most patients. Grade 2, a weak recommendation by ACCP, means that ACCP is less certain of the magnitude of the benefits and risks, burden, costs, and thus their relative impact. Grade 2 suggestions require more judicious application, particularly considering patient values and preferences, as well as cost when resource limitations are considered to be important. Randomized controlled trials (RCT) and observational studies with very large effects are considered to be of high quality ("A") evidence. Downgraded RCT or upgraded observational studies are generally considered to be of moderate quality ("B") and observational studies or RCT with major limitations are classified as being low quality ("C"). Therefore, RCT are high quality (A) evidence, but can be downgraded to B or C as a result of poor design and trial conduct, imprecision, inconsistent results, indirectness or a high likelihood for reporting bias. Thus, recommendations made by the ACCP panel members fall into one of the following categories: 1A, 1B, 1C, 2A, 2B, or 2C.[2]

ACCP RECOMMENDATIONS FOR PROPHYLAXIS OF VENOUS THROMBOEMBOLISM (VTE)

VTE PROPHYLAXIS IN ORTHOPEDIC SURGERY

ACCP guidelines recommend *Arixtra* in patients undergoing:

1. Elective hip replacement (*Arixtra* 2.5 mg started 6-24 hours after surgery and continued for at least 10 days) (Grade 1A). [1,3]
   - Note: This dosing schedule is contrary to the *Arixtra* Prescribing Information. In DVT prophylaxis following hip fracture, or hip or knee replacement surgeries, *Arixtra* is indicated to be administered after hemostasis has been established with an initial subcutaneous dose of *Arixtra* 2.5 mg given 6 to 8 hours after surgery.[4]
   - Low Molecular Weight Heparins (LMWH) or adjusted-dose Vitamin K Antagonists (VKA) may also be used in these patients (each Grade 1A). [1,3]
   - Extended prophylaxis in patients undergoing total hip replacement includes *Arixtra* (Grade 1C), LMWH (Grade 1A) or VKA (Grade 1B). Duration of therapy for extended prophylaxis is >10 days and ≤ 35 days after surgery (Grade 1A).[1,3]
2. Total knee replacement (therapy for at least 10 days) (Grade 1A).[1,3]
   - LMWH or adjusted-dose VKA may be used in these patients (each Grade 1A). [1,3]
   - Extended prophylaxis in patients undergoing total knee replacement includes *Arixtra*, LMWH, or VKA (each Grade 1C). Duration of therapy for extended prophylaxis is >10 days and ≤ 35 days after surgery (Grade 2B).[1,3]
3. Hip fracture surgery (therapy for at least 10 days) (Grade 1A).
   - LMWH, adjusted-dose VKA or low-dose unfractionated heparin (LDUH) may be used in these patients (each Grade 1B).[1,3]
   - Extended prophylaxis in hip fracture surgery includes *Arixtra* (Grade 1A), LMWH (Grade 1C), or a VKA (Grade 1C). Duration of therapy for extended prophylaxis is >10 days and ≤ 35 days after surgery (Grade 1A). [1,3]

The ACCP guidelines also recommend to initiate *Arixtra* therapy starting 6-8 hours after surgery or on the next day (Grade 1A).[1,3]

- Note: This dosing schedule is contrary to the *Arixtra* Prescribing Information. In DVT prophylaxis following hip fracture, or hip or knee replacement surgeries, *Arixtra* is indicated to be administered after hemostasis has been established with an initial subcutaneous dose of *Arixtra* 2.5 mg given 6 to 8 hours after surgery.[4]

VTE PROPHYLAXIS IN GENERAL, VASCULAR, GYNECOLOGICAL, UROLOGIC, LAPAROSCOPIC, BARIATRIC AND THORACIC SURGERIES

ACCP guidelines recommend *Arixtra* in patients undergoing:

1. Moderate risk general surgery patients who are undergoing a major procedure for benign disease (Grade 1A).[1,3]
   - LMWH or LDUH may also be used in these patients (each Grade 1A).[1,3]
2. Higher-risk general surgery patients who are undergoing a major procedure for cancer (Grade 1A).[1,3]
   - LMWH or LDUH three times daily may also be used in these patients (each Grade 1A).[1,3]
3. General surgery patients with multiple risk factors for VTE who are thought to be at particularly high risk. ACCP recommends the use of *Arixtra* combined with the optimal use of graduated compression stockings (GCS) and/ or intermittent pneumatic compression (IPC) (Grade 1C).[1,3]
   - LMWH or LDUH three times daily may also be combined with GCS/IPC in these patients (each Grade 1C).[1,3]

4. Major vascular surgery who have additional VTE risk factors (Grade 1C).[1,3]
   - LMWH or LDUH may also be used in these patients (each Grade 1C).[1,3]
5. Extensive gynecological surgery for malignancy with additional VTE risk factors (Grade 1C).[1,3]
   - LMWH, LDUH three times daily or IPC, started just prior to surgery and used continuously while the patient is not ambulatory may also be used in these patients (each Grade 1A).[1,3]
   - LMWH or LDUH plus GCS or IPC are other alternatives in these patients (each Grade 1C).[1,3]
6. Major, open urologic procedures with or without GCS and/ or IPC (each Grade 1C).[1,3]
   - LDUH twice daily or three times daily (Grade 1B), GCS and/ or IPC started just prior to surgery and used continuously while the patient is not ambulating (Grade 1B), LMWH (Grade 1C) or combination of LMWH or LDUH plus GCS and/ or IPC (Grade 1C) may also be used in these patients.[1,3]
7. Laparoscopic procedures, with additional VTE risk factors, with or without IPC and/ or GCS (Grade 1C).[1,3]
   - LMWH, LDUH, IPC or GCS may also be used in these patients (each Grade 1C).[1,3]
8. Inpatient bariatric surgery with or without IPC (Grade 1C).[1,3]
   - LMWH, LDUH three times daily or combination of one of these agents plus optimally used IPC may also be used in these patients (each Grade 1C).[1,3]
9. Major thoracic surgery (Grade 1C).[1,3]
   - LMWH or LDUH may be used in these patients (each Grade 1C).[1,3]

ACCP RECOMMENDATIONS FOR TREATMENT OF VENOUS THROMBOEMBOLISM (VTE)

1. Initial anticoagulation of acute DVT of the leg or PE: In patients with objectively confirmed DVT or PE, ACCP recommends short-term treatment with *Arixtra* (Grade 1A).[1,5]
   - SC LMWH, IV UFH, monitored SC UFH, or fixed dose SC UFH may also be used in these patients (each Grade 1A).
   - Patients with acute PE should be routinely assessed for treatment with thrombolytic therapy.[1,5]
2. Initial anticoagulation of acute DVT of the leg or PE: In patients with acute DVT/ PE, initiation of a VKA plus *Arixtra*, LMWH, or UFH is recommended on the first treatment day rather than delayed initiation of VKA (Grade 1A).[1,5]
   - ACCP recommends initial treatment of acute DVT or PE with *Arixtra*, LMWH, or UFH for at least 5 days and until the international normalized ratio (INR) is $\geq$ 2.0 for 24 hours (each Grade 1C).[1,5]
3. In patients with acute upper extremity DVT, ACCP recommends initial treatment with *Arixtra*, LMWH, or UFH as described in treatment of DVT of the leg (each Grade 1C).[1,5]
4. In patients with massive PE, in other situations where there is concern about SC absorption, or in patients in whom thrombolytic therapy is being considered or planned, ACCP recommends IV UFH over SC *Arixtra*, SC LMWH, or SC UFH (each Grade 2C).[1,5]

ACCP RECOMMENDATIONS FOR VENOUS THROMBOEMBOLISM (VTE) PROPHYLAXIS IN MEDICALLY ILL PATIENTS

1. ACCP recommends *Arixtra* for VTE prophylaxis in acutely ill medical patients admitted to the hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurological disease, or inflammatory bowel disease (Grade 1A).[1,3]
   - Low molecular weight heparin (LMWH) or low-dose unfractionated heparin (LDUH) may also be used in these patients (each Grade 1A).[1,3]

ACCP RECOMMENDATIONS FOR THE TREATMENT OF HIT

1. In patients with strongly suspected or confirmed HIT (with or without thrombosis), ACCP recommends the use of an alternative, non-heparin anticoagulant over the further use of unfractionated heparin (UFH), low-molecular weight heparins (LMWH), or initiation/continuation of a vitamin K antagonist (Grade 1B).[1,6]
   - *Arixtra* was assigned a Grade 2C recommendation for use in patients with strongly suspected or confirmed HIT (with or without thrombosis).[1,6]
   - Additional non-heparin anticoagulants recommended for use in patients with strongly suspected or confirmed HIT include danaparoid (Grade 1B), lepirudin (Grade 1C), argatroban (Grade 1C) and bivalirudin (Grade 2C).[1,6]
   - Argatroban is licensed to Encysive (formerly Texas Biotechnology Corporation, TBC) and sub-licensed to GlaxoSmithKline (GSK), co-developed by TBC and GSK, and sold and marketed by GSK.

ACCP RECOMMENDATIONS FOR BREASTFEEDING WOMEN

ACCP Recommends:

1. Alternative anticoagulants for breastfeeding women over pentasaccharides such as *Arixtra* (Grade 2C).[1,7]

ACCP RECOMMENDATIONS FOR NON-ST-ELEVATION MYOCARDIAL INFARCTION (NSTEMI)

ACCP recommends:

1. *Arixtra* over no anticoagulation at all in NSTEMI patients (Grade 1A)[1,8]
   - UFH, LMWH or bivalirudin may also be used in these patients (each Grade 1A)[1,8]
2. For patients undergoing early conservative or delayed invasive strategy, *Arixtra* is recommended over enoxaparin (Grade 1A).[1,8]
3. In patients undergoing early invasive strategy (e.g., PCI) UFH plus a glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitor is recommended over either *Arixtra* or LMWH (Grade 1B).[1,8]
4. In patients treated with upstream *Arixtra* and undergoing PCI, additional IV boluses of UFH (50 – 60 U/kg) are recommended as well as additional IV doses of *Arixtra* (Grade 1B).[1,8]
   - *Arixtra* 2.5 mg if GP IIb/IIIa inhibitor administered; 5 mg if no GP IIb/IIIa inhibitor (Grade 1B).[1,8]
   - PCI operators should regularly flush the catheters with UFH during the procedure as well.[1,8]

ACCP RECOMMENDATIONS FOR ST-ELEVATION MYOCARDIAL INFARCTION (STEMI)

ACCP recommends:

1. The use of *Arixtra* in STEMI patients not receiving reperfusion therapy (e.g., PCI) over no therapy (Grade 1A).[1,9]
   - The recommended dosing of *Arixtra* is 2.5 mg IV for the first dose then SC once daily up to 9 days.[1,9]
2. Against the use of *Arixtra* for STEMI patients receiving primary PCI (Grade 1A).[1,9]
3. The use of *Arixtra* in STEMI patients receiving fibrinolytic therapy and thought not to have an indication for anticoagulation over no therapy (Grade 1B).[1,9]
   - The recommended dosing of *Arixtra* is 2.5 mg IV for the first dose then SC once daily up to 9 days.[1,9]
4. *Arixtra* could be used as an alternative to UFH in STEMI patients receiving fibrinolytic therapy and thought to have an indication for anticoagulation (Grade 2B).[1,9]

- The recommended dosing of *Arixtra* is 2.5 mg IV for the first dose then SC once daily up to 9 days.[1,9]

Some information contained in this response is outside the approved Prescribing Information. This product is not approved for the use described. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

REFERENCE(S)

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